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WANG, CHANG YU	
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1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,472	CHARETTE, MARC F.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/26/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-32,34-38,43,44,46,48 and 51-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-32, 34-38, 43, 44, 46, 48 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed 9/26/07 is acknowledged. Claims 1-26, 33, 39-42, 45, 47 and 49-50 are cancelled. Claims 27, 34-35, 46 and 48 are amended. Claims 27-32, 34-38, 43, 44, 46, 48 and 51-53 are pending in this application and under examination in this office action.

2. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

3. Applicant's arguments filed on 9/27/07 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

4. The rejection of claims 34 and 35 under 35 U.S.C. 112, second paragraph, for being indefinite because of the recitation of a broader range followed by a narrow range is withdrawn in response to Applicant's amendment to the claims by reciting residues 293-341 of SEQ ID NO:2

The rejection of claims 27-32, 34-38, 43, 44, 48, 51-53 under 35 U.S.C. 102 (e) for being anticipated by U. S. Patent No. 6723698 (Rueger et al. issued on April 20, 2004, effective filling date September 25, 1997) is withdrawn in response to Applicant's amendment to the claims by reciting a step of determining the existence of memory dysfunction.

Claim Rejections/Objections Maintained

In view of the amendment filed on 9/26/07, the following rejections are maintained.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-32, 34-38, 43, 44, 46, 48 and 51-53 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for up-regulating the expression of N-CAM and L1 in NG108-15 cells and increasing dendritic arbors of 7-14 DIV cultured hippocampal neurons with OP-1 (BMP-7) protein of SEQ ID NO:2, does not reasonably provide enablement for general methods for reducing memory dysfunction associated with damaged hippocampal tissues and caused by permanent or transient global ischemia comprising determining the existence of memory dysfunction and administering a structurally ill-defined morphogen merely comprising a conserved C-terminal seven-cysteine skeleton that is at least about 60% identical and 70% homologous to residues 330-431 of human OP-1 (SEQ ID NO:2) or fragments thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The rejection is maintained for the reasons made of record in the office action mailed 6/27/07, and as follows.

At p. 5-6 of the response, Applicant argues that the claims are enabled because US6506729 and Morrison et al. (Science 1997. 278: 412-419) have been shown functional recovery in the CNS impaired by stroke and synaptic regeneration in vitro by a morphogen. Applicant further argues that the instant claims are enabled because the instant invention is an analogous observation for damage caused by ischemia. Applicant's arguments have been fully considered but they are not persuasive.

In contrast to Applicant's assertion, the instant claims are not enabled for the full scope of the invention because the instant claims as currently written encompass uncharacterized and undefined memory dysfunction and memory dysfunction or deficit is a complex process and its cause or process is not clear; i.e. it is not only due to neuronal damage or neuronal loss. Based on the prior art and the specification, the instant claims are only enabling for neurite outgrowth or neuronal protection against neuronal damage caused by ischemia or caused by other mechanisms such as malnutrition, anorexia or memory deficit caused by hippocampal neuronal damage or loss. However, the instant claims are not limited to the enablement as set forth above since memory dysfunction is only a general term and is not clear what is encompassed. It is unpredictable whether the claimed method can truly reduce memory dysfunction since neither prior art nor the specification provides evidence to show that morphogens are predictably effective in such broad and undefined and uncharacterized memory dysfunction.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that: "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, it is unpredictable whether the claimed method can reduce a general term of undefined and uncharacterized memory dysfunction; and the experimentation left to those skilled in the art is extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation.

At p. 6 of the response, Applicant argues that the issued patents recite morphogen proteins with the homology as recited in the instant claims and they are

presumed valid and it is the examiner's burden to show that they are enabled. Applicant's arguments have been fully considered but they are not persuasive.

As acknowledged by Applicant, each application is judged by its own merit. In this case, since neither the specification nor the prior art shows that the claimed morphogens with limited homology as recited in instant claims are effective in treatment of reducing undefined or uncharacterized memory dysfunction, it is unpredictable whether these claimed morphogens with limited homology would truly work in the claimed method.

"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)" See MPEP § 2164.03

"According to In re Bowen, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. This standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments. See also In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (citing In re Bundy, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981))" See MPEP 2164.04 [R1].

Accordingly, the rejection of claims 27-32, 34-38, 43, 44, 46, 48 and 51-53 under 35 U.S.C. §112, first paragraph, because the specification does not enable the invention commensurate in scope with the claims is maintained.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 27-32, 34-38, 43, 44, 46, 48 and 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rueger et al. (US Patent No. 6723698, issued on April 20, 2004, priority September 25, 1997) in view of Bachevalier et al. (Hippocampus. 1996. 6: 553-560), Contestabile et al. (J. Neurosci. Res. 1990. 26: 483-7), Simonsen et al. (Scand J. Work Environ. Health. 1994. 20: 1-12) and Gillette-Guyonnet et al. (Am. J. Clin. Nutr. 2000. 71:637S-642S) and an evidentiary reference Holownia et al. (Mater Med. Pol. 1994 Jan-Mar; 26: 25-7). The rejection is maintained for the reasons made of record in the office action mailed 6/27/07, and as follows.

At p. 7-8 of the response, Applicant argues that instant claims have been amended to recite the step of determining the existence of memory dysfunction and neither the '698 patent nor the secondary references teach the association of memory dysfunction with hippocampal neuronal damage. Applicant further argues that the combined references does not render the claimed invention obvious because none of the references teach the association of memory dysfunction with hippocampal neuronal

damage and Constabile teaches ibotenic not ammonia and Simonesen teaches neurotoxins and Gillette-Guyonnet teaches weight loss by anorexia in AD.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, as previously made of record, the '698 patent teaches hypoxia and ischemia-reperfusion, which is a permanent or transient global ischemia as recited in instant claim 27 (see col.36, lines 36-67). The '698 patent also teaches administration of OP-1 to prevent neuronal cell death caused by ischemia (as it relates to claim 27; see col.36 example 11), traumatic brain injury (col. 53, example 20). The hippocampal tissue damage is an intrinsic result of global ischemia and cerebral ischemia as evidenced by Bachevalier et al. (see p. 553, abstract; p. 554 and p. 557). Bachevalier et al. teach that patients with global ischemia and cerebral ischemia also have memory

deficits include memory impairment caused by hippocampal damages. Although the '698 does not explicitly teach the step of determining the existence of memory dysfunction, Bachevalier et al. teach the step of determining the existence of memory deficit or dysfunction (p. 554-556). Furthermore, brain ischemia is also intrinsically accompanied with an increased concentration of ammonia and a decrease of glutamate dehydrogenase activity, which are the factors for neurotoxicity and neuronal loss and memory deficit, as evidenced by Holownia et al. (Mater Med. Pol. 1994 Jan-Mar; 26: 25-7). Thus, in contrast to Applicant's arguments, the examiner asserts that the claimed invention is obvious over the applied references because the '698 patent teaches administration of OP-1 to prevent neuronal cell death caused by ischemia and memory deficit and the hippocampal tissue damage are intrinsic result of global ischemia and cerebral ischemia and Bachevalier teaches the step of determining the existence of memory deficit caused by global or cerebral ischemia.

"Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)" See MPEP § 2143. 01-I.

Although the '698 patent does not teach the damaged hippocampal tissue damage caused by ibotenic acid, ammonia, and formaldehyde as recited in instant claim 46, Contestabile et al. and Simonsen et al. teach ibotenic acid and formaldehyde as a neurotoxin to cause neuronal damage (see p. 483, abstract of Contestabile and p. 637S, abstract of Simonsen) and ammonia is the cause of neurotoxicity of cerebral ischemia and memory deficit as taught by Bachevalier.

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980); see also *In re Crockett*, 279 F.2d

274, 126 USPQ 186 (CCPA 1960) and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992). See MPEP § 2144.06.

"The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

Thus, it is obvious to a skilled artisan at the time the instant invention was made to administer OP-1 to a patient to protect neurons against neuronal damage in memory deficit associated with hippocampal neuronal damage caused by neurotoxins such as ibotenic acid, ammonia and formaldehyde by since OP-1 has been shown to be neuroprotective on neuronal damage caused by ischemia/chemical/physical trauma/neurotoxin and patients with hippocampal neuronal loss in cerebral ischemia is also accompanied with memory deficit.

In addition, although the '698 patent does not teach neuronal loss caused by anorexia, Gillette-Guyonnet et al. teach that weight loss is associated with Alzheimer's disease (a disease that is characterized by hippocampal neuronal loss and damage and also memory deficit) and anoxreia is associated with AD (see p. 319, abstract of Gillette-Guyonnet). Thus, it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to administer OP-1 to reduce neuronal damage in memory deficit caused by malnutrition due to anorexia since OP-1 has been shown to be neuroprotective on neuronal damage caused by malnutrition as taught by Rueger et al. ('698) and anorexia is associated with AD, which is characterized as memory deficit and also hippocampal damage. The person of ordinary skill in the art would have been motivated to administer OP-1 to the damaged hippocampus caused by malnutrition or anorexia because OP-1 has been shown to enhance neuronal

survival in the hippocampus in patients with ischemia and ischemia is intrinsically accompanied with memory deficit and hippocampal damage.

New Grounds of Rejection Necessitated by the Amendment

The following rejections are new grounds of rejections necessitated by the amendment filed on 9/26/07.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The rejection is reinstated and maintained for the reasons made of record in the office action mailed on 11/03/06, and as follows.

The claims as amended are directed to a method for reducing memory dysfunction associated with damaged hippocampal tissue in a mammal comprising determining the existence of memory dysfunction and administering a morphogen comprising residues 293-431 of SEQ ID NO:2. The instant claims now recite the limitation of residues 293-431 of SEQ ID NO:2, which was not clearly disclosed in the

specification and claim as filed, and now change the scope of the instant disclosure as filed. Such limitation recited in the present claims, which did not appear in the specification or original claims, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

The specification fails to disclose the limitation of "a morphogen comprising residues 293-431 of SEQ ID NO:2" as recited in instant claims 34 and 35 because the specification only discloses 30-292, 330-431, and 48-292 of SEQ ID NO:2 on p.12 of the specfiication. Accordingly, in the absence of sufficient recitation of residues 293-431 of SEQ ID NO:2, the specification does not provide adequate written description to support the morphogen comprising residues 293-431 of SEQ ID NO:2 as recited in instant claims 34 and 35. Support is not found for the morphogen comprising residues 293-431 of SEQ ID NO:2 as disclosed in the original specification and thus the recitation constitutes new matter absent evidence for its support. Applicant is required to cancel the new matter in the reply to this office action. Alternatively, Applicant is invited to clearly point out the written support for the instant limitation.

Conclusion

8. NO CLAIM IS ALLOWED.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is.(571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
December 4, 2007

CHRISTINE J. SAOUD
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